Synthetic Organic Chemicals

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Halogenated Phenolphthaleins in X-Ray Examinations of the Gall Bladder

A SUBJECT of interest to organic chemists, and one which has had little attention in the chemical journals, is the use of halogenated phenolphthaleins in connection with the x-ray visualization of the gall bladder. The photography of this part of the anatomy has become so important in the last few years that it has been dignified by giving it a name—cholecystography. The technique of the methods now in general use was developed largely by Dr. Graham and his co-workers at Washington University, although many other institutions of the country also shared in the pioneer work.

For the benefit of those who only dimly remember that we have such an appendage, it may be stated that the gall bladder is a small sac which acts as a reservoir for storing and concentrating the bile formed in the liver. When bile is needed in the course of the digestive process, it is discharged from this sac through short tubular ducts into the small intestine. If the gall bladder fails to function in the normal manner, the digestion is disturbed, the bile becomes thicker, involved pathological changes begin, and sometimes an operation is necessary to correct the condition. Gallstones are often formed, and, although their presence may cause no discomfort, they are a potential source of trouble in adhering to the inner surface or blocking some of the biliary ducts.

The successful photography of any part of the body by x-rays depends on the amount of contrast obtained in the picture, which is determined by the opacity of the part to x-rays. One of the greatest advances in the study of the stomach and intestines was made when it was shown that barium sulphate, administered orally, is practically opaque to x-rays. By taking a series of photographs, the progress of food through the alimentary tract can easily be followed. A search for a similar material that would be absorbed in the bile, and thus make the gall bladder opaque to x-rays, resulted in a study of the halogenated phenolphthaleins. These compounds were chosen because it was well known that phenolphthalein taken internally appeared in the bile, and that the halogen elements were relatively opaque to x-rays.

The first compound that showed promise was tetra-bromo-phenolphthalein, which, after literally having been tried out on the dog, was given to the patient intravenously in the form of a water solution of the sodium salt. About four to six hours after the injections, x-ray photographs were taken, in which the gall bladder began to show as a faint shadow. During the time from the

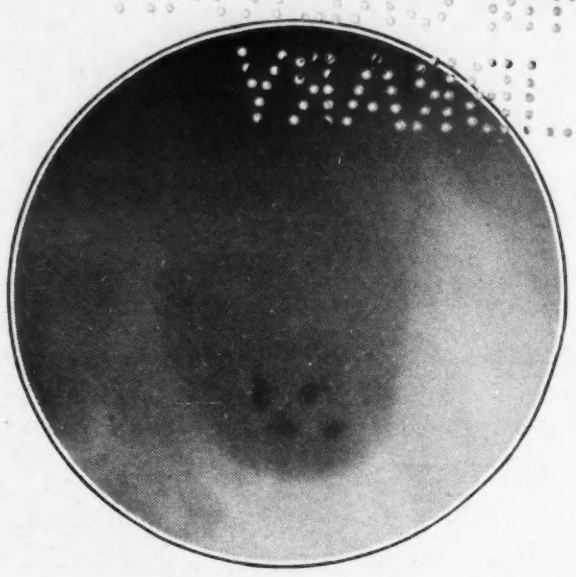


Figure 1

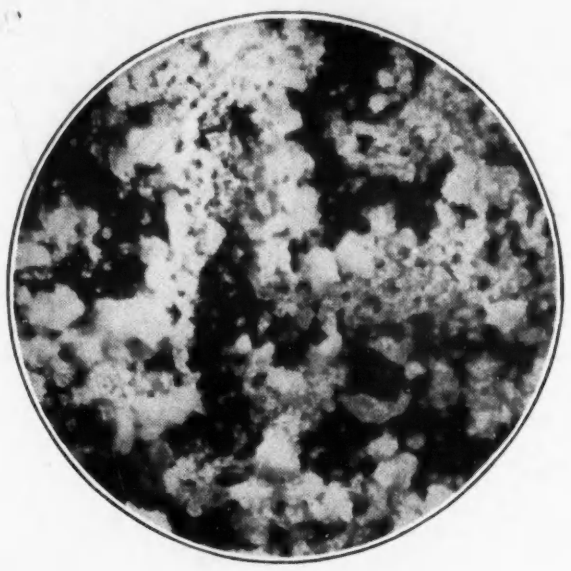


Figure 2

eighth to the twelfth hour, the shape and size of the shadow were quite clearly defined, showing that the dye had found its way to the bile. Figure 1 shows a gall bladder shadow obtained by this method, in which four gallstones can be seen. After a meal containing fatty foods, the shadow became smaller and less distinct, showing that the bile was functioning in the normal manner.

When only faint shadows or none at all appeared, it was apparent that the secretion of bile was being hindered, and operations in most of these cases showed obstructions in the ducts, pressure by other organs, or pathological conditions which prevented passage of the bile. Some types of gallstones which are invisible in an ordinary x-ray photograph can be distinguished by their transparency when surrounded by the dye-containing bile.

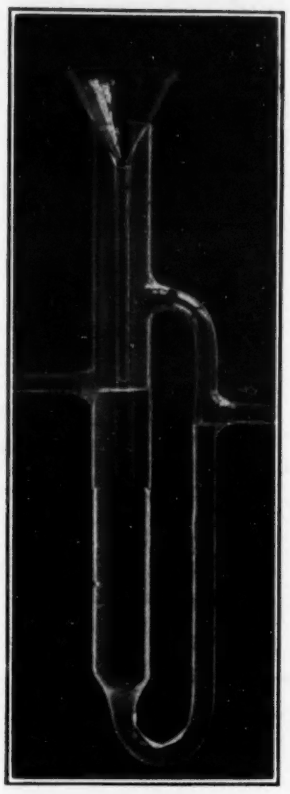
The bromo-compound, unfortunately, had several undesirable features, among which was a marked lowering of the patient's blood pressure. The pure iodo-compound had few of these unpleasant features, since it was more opaque to x-rays on account of its higher molecular weight, and could therefore be used in smaller doses. The principal difficulty with this compound was in its purification, which required tedious crystallizations. In fact, it was once discarded by the investigators, in favor of the bromo-compound, on account of the impurities which their iodo-compound contained. Methods for its purification were soon worked out by the Kodak Research Laboratories, which were the first to market the compound in crystalline form for medical purposes.

The change to the tetraiodophenolphthalein sodium salt, with its less disturbing effects, made administration much simpler. In most cases now, the patient calls at the doctor's office in the evening, has the dye given him either orally or intravenously, and then returns the next morning for the x-ray photographs. The problem of oral administration was partly solved by using sodium carbonate to prevent precipitation of the acid form of the dye in the stomach, and by using capsules which would not dissolve until the small intestine was reached.

The sodium salt of tetraiodophenolphthalein crystallizes in short pale blue prisms, the microstructure of which is shown in Figure 2. The air dry crystals contain about 55% of iodine, 5% of sodium, and 7% of water, which corresponds roughly to a hydrate containing 3½ molecules of water. The sodium salt dissolves to the extent of 12% in water at 20°, the solubility increasing to 40% at 80°. It is also easily soluble in alcohol.

A Continuous Separator for Organic Liquids.

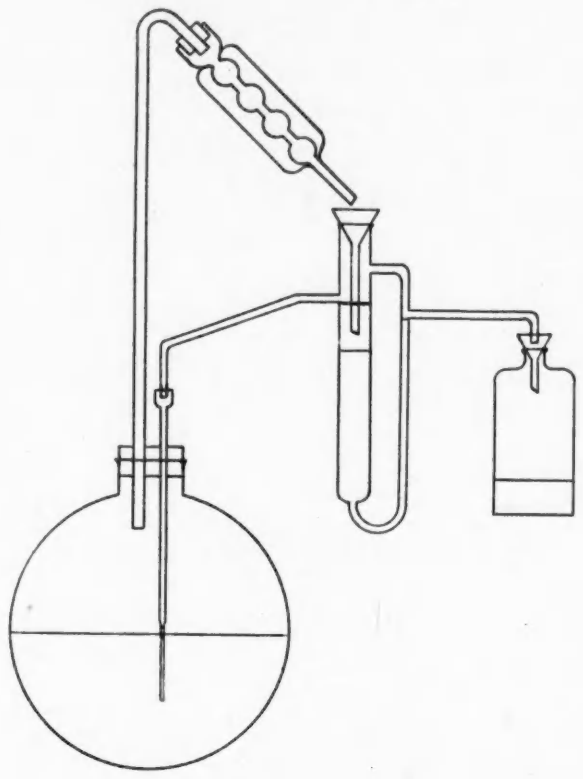
An automatic separator which finds many applications in organic preparations is shown in the photograph below. It can be used advantageously to separate two immiscible or partially miscible liquids which differ in density by more than 2 per cent.



By combining it with an ordinary distillation apparatus, as shown in the diagram, one of the liquids can be returned to the boiling flask for redistillation without interrupting the operation. The heavier liquid can be returned by reversing the connections to the delivery so that the lower one leads to the flask and the upper to the receiver.

The construction of such a separator is quite simple, as can be seen from the diagram. The size which we have found most convenient for our work measures about 200 mm. in length and is made of 20 mm. and 5 mm. Pyrex tubing. The side arm on the smaller tube is placed about 10 mm. (from center to center) below the one on the larger tube. Both of these arms should be at right angles to the vertical tubes, and must not incline upward at any part of their length.

Before the separation is begun, the apparatus is partly filled with the heavier liquid to prevent the passage of the lighter liquid into the narrow limb. The suspension of liquids is then introduced through a funnel, which extends a short distance below the side arm. A description of this apparatus, together with some of its uses, is given in J. A. C. S. *43*, 366 (1921), but the comments of visitors to our laboratory lead us to believe that its uses are not as well known as its convenience would warrant.



We have used this apparatus very successfully in the preparation or purification of the following compounds: aniline, quinoline, salicylaldehyde, butyl ether, anhydrous oxalic acid, ethyl and butyl oxalates, and many others. It can also be employed for steam distillation without live steam, the separated water being continuously returned to the distilling flask.

New Chemicals

The following preparations have been added to our list since the last issue of this pamphlet:

Acetoacetanilide (Prac.)
*5-Amino-1.3-dimethylbenzene
n-Amyl Alcohol (Tech.)
Sec.-Amyl Alcohol (Tech.)
Amylene Dichloride (Tech.)
*Benzenesulfonic Acid
Sec.-Butyl Carbinol (Tech.)
4-Chloro-2-nitroaniline Hydrochloride (Prac.)
*2-Chloropropyl Acetate
2.5-Dichloroaniline (Prac.)

Diethyl Carbinol (Tech.)
*G Salt (Recryst.)
5-Nitro-2-aminoanisole (Prac.)
5-Nitro-2-aminotoluene (Prac.)
o-Nitroaniline (Prac.)
*5-Nitro-1.3-dimethylbenzene
*Nitrofluorene (Prac.)
*Pyridine Hydrochloride
*2.4.6-Tribromoanisole
*2.4.6-Tribromophenyl Acetate

**Made or purified in the Kodak Research Laboratories.*

Organic Chemicals as Analytical Reagents

IV Reagents for Cobalt

Dimethylglyoxime

Braley and Hobart, J. A. C. S. *43*, 482 (1921)

Cobalt solutions acidified with acetic acid and sodium acetate give a brown coloration with dimethylglyoxime. This permits a colorimetric method for cobalt in filtrates from nickel precipitates, after interfering substances such as copper and iron have been removed.

Dinitrosoresorcinol

Orndorff and Nichols, J. A. C. S. *45*, 1439 (1923)

An aqueous solution of dinitrosoresorcinol precipitates cobalt quantitatively from acid solutions. Fifty cc. of the solution to be analyzed, containing about 0.02 gm. cobalt is treated with 1 cc. of hydrochloric acid (s. g. 1.17) and then warmed with 300 cc. of water containing 0.3 gm. of the reagent. The red colored solution is stirred with the addition of sodium acetate and then digested over a low flame for fifteen minutes. The voluminous, brown-red precipitate is washed with 1% hydrochloric acid and then dried at 125°. Copper, iron, and large amounts of nickel must be removed before the determination.

Nitroso-β-Naphthol

Eder, Chem. Zeit. *46*, 430 (1922) see also C. A. *16*, 2280 (1922)

Steel turnings are dissolved in sulphuric acid, and the iron oxidized with nitric acid. After evaporating to a syrup, diluting with water and boiling, the iron is precipitated by the addition of zinc oxide. To an aliquot portion of the filtrate is added a small amount of hydrochloric acid, and the solution is concentrated by evaporation. After diluting and boiling, the solution is treated with twice the theoretical quantity of nitroso-β-naphthol in hot 50% acetic acid solution. The precipitate is allowed to stand and then finally washed with hydrochloric acid and water. It is ignited with a little oxalic acid and weighed as Co_2O_3.

Jones, Analyst *43*, 317 (1918) gives details of a colorimetric method for determining small amounts of cobalt using nitroso-β-naphthol.

Nitroso-R-Salt

van Klooster, J. A. C. S. *43*, 746 (1921)

A solution of 0.5 gm. of nitroso-R-salt in 100 cc. of water is a sensitive reagent for cobalt. To 2 cc. of the cobalt solution is added 1 gm. of sodium acetate and 2 cc. of the reagent. After heating to boiling, 1 cc. of nitric acid is added and heating continued for 1 minute. A permanent red color indicates cobalt, as the colors produced with other metals are destroyed by the acid.

Phenylthiohydantoic Acid

Willard and Hall J. A. C. S. *44*, 2219 (1922)

This reagent can be used in slightly ammoniacal solution to precipitate cobalt from solutions containing aluminum, chromium, vanadium, uranium, tungsten, molybdenum, arsenic, titanium, zinc, manganese, calcium, and magnesium. Iron and nickel are partially precipitated but may be easily removed before the cobalt analysis is made.